Express Mail No. EV687637302US

APPELLANTS' BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	09/960,708
	Confirmation Number	4284
	Attorney Docket No.	STAN-201
	Filing Date	September 19, 2001
	First Named Inventor	Crabtree, Gerald R.
	Examiner	McGarry, Sean
	Group Art	1635
	Title: *Methods and Compositions for Modulating Angiogenesis*	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated August 12, 2005. No claims have been allowed. Claims 8-11, 15-18, 35-44, 46 and 47 are pending and appealed herein. A Notice of Appeal was filed on January 31, 2006. In view of the enclosed petition for a 1-month extension of time, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815, reference no. STAN-201 to cover the fee required under 37 C.F.R. §1.17(c) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, reference no. STAN-201.

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TABLE OF CONTENTS

REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Stanford University.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on September 19, 2001 with Claims 1-29. During the course of prosecution, Claims 30-47 were added and Claims 1-7, 12-14, 19-34, and 45 were canceled. Accordingly, Claims 8-11, 15-18, 35-44, 46 and 47 are pending in the present application, all of which stand rejected. All of the rejected claims are appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to inhibiting unwanted angiogenesis/tumor growth in a host by administering an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent.

Below is a description of each appealed claim and where support for each can be found in the specification.

Claim 8 claims a method of inhibiting angiogenesis/vascular development in a host having a condition associated with unwanted angiogenesis, the method including systemically administering to the host an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent (see specification at page 8, line 23 to page 9, line 11).

Claim 9 claims the method according to Claim 8 in which the agent is an NF-ATc

antagonist (see specification at page 2, lines 18-20).

Claim 10 claims the method according to Claim 9 in which the agent inhibits phosphorylation of NF-ATc (see specification at page 6, line 13).

Claim 11 claims the method according to Claim 10 in which the agent inhibits NF-ATc phosphorylation by binding to calcineurin (see specification at page 6, lines 23-25).

Claim 15 claims a method of inhibiting tumor growth in a host having a neoplastic disease condition, the method including systemically administering to the host having a neoplastic disease condition an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent (see specification at page 8, line 23 to page 9, line 11; and page 10, line 27 to page 11, line 1).

Claim 16 claims the method according to Claim 15 in which the agent is an NF-ATc antagonist (see specification at page 2, lines 18-20).

Claim 17 claims the method according to Claim 16 in which the agent inhibits phosphorylation of NF-ATc (see specification at page 6, line 13).

Claim 18 claims the method according to Claim 16 in which the agent inhibits NF-ATc phosphorylation by binding to calcineurin (see specification at page 6, lines 23-25).

Claim 35 claims the method according to Claim 8 in which the agent is FK506 or a synthetic mimetic thereof (see specification at page 6, lines 26-28).

Claim 36 claims the method according to Claim 8 in which the agent is rapamycin or a synthetic mimetic thereof (see specification at page 6, lines 26-28).

Claim 37 claims the method according to Claim 8 in which the agent is a cyclosporin (see specification at page 6, line 29 to page 7, line 5).

Claim 38 claims the method according to Claim 37 in which the cyclosporin is cyclosporin A (see specification at page 6, line 29).

Claim 39 claims the method according to Claim 38 in which the cyclosporin is a synthetic derivative or mimetic of cyclosporin A (see specification at page 6, line 29 to page 7 line 1).

Claim 40 claims the method according to Claim 15 in which the agent is FK506 or a synthetic mimetic thereof (see specification at page 6, lines 26-28).

Claim 41 claims the method according to Claim 15 in which the agent is rapamycin or a synthetic mimetic thereof (see specification at page 6, lines 26-28).

Claim 42 claims the method according to Claim 15 in which the agent is a

cyclosporin (see specification at page 6, line 29 to page 7, line 5).

Claim 43 claims the method according to Claim 42 in which the cyclosporin is cyclosporin A (see specification at page 6, line 29).

Claim 44 claims the method according to Claim 42 in which the cyclosporin is a synthetic derivative or mimetic of cyclosporin A (see specification at page 6, line 29 to page 7 line 1).

Claim 46 claims a method of inhibiting angiogenesis/vascular development in a host having a condition associated with unwanted angiogenesis, the method including administering to the host an effective amount of a cyclosporin to inhibit angiogenesis/vascular development (see specification at: page 8, line 23 to page 9, line 11; and page 6, line 29 to page 7, line 5).

Claim 47 claims a method of inhibiting tumor growth in a host having a neoplastic disease condition, the method including administering to the host an effective amount of a cyclosporin to inhibit tumor growth (see specification at: page 8, line 23 to page 9, line 11; page 10, line 27 to page 11, line 1; and page 6, line 29 to page 7, line 5).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 8-11, 15-18, 35, 37, 39, 40 and 44 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Jiang et al. (Carcinogenesis 1993 14:67).

II. Claims 36-44, 46 and 47 stand rejected under 35 U.S.C. § 103(a) as being obvious over Jiang et al. (Carcinogenesis 1993 14:67) in view of Flanagan et al. (Nature 1991 352:803).

ARGUMENT

In the arguments set forth below, the Appellants will argue the rejected claims in Groups as follows:

Group I: Claims 8-11 and 35-39, drawn to a method of inhibiting angiogenesis in a host having a condition associated with unwanted angiogenesis by administering to the subject an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent;

Group II: Claims 15-18 and 40-44, drawn to a method of inhibiting tumor growth in a host having a neoplastic disease condition by administering to the subject an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent;

Group III: Claim 46, drawn to a drawn to a method of inhibiting angiogenesis in a host having a condition associated with unwanted angiogenesis by administering to the subject an effective amount of a cyclosporin; and

Group IV: Claim 47, drawn to a method of inhibiting tumor growth in a host having a neoplastic disease condition by administering to the subject an effective amount of a cyclosporin.

I. Claims 8-11, 15-18, 35, 37, 39, 40 and 44 are not anticipated under 35 U.S.C. § 102(b) by Jiang et al. (Carcinogenesis 1993 14:67).

Group I: Claims 8-11, 35, 37 and 39

As described above, independent Claim 8 is drawn to methods of inhibiting angiogenesis in a host having a condition associated with unwanted angiogenesis by administering to the subject an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent. Claims 9-11, 35, 37 and 39 that dependent from Claims 8 are drawn to the use of specific Ca^{2+}/calcineurin/NF-ATc inhibitory agents (e.g., cyclosporin, FK506, rapamycin, or derivatives thereof).

The Examiner has rejected the claims of this Group as being anticipated by Jiang et al. In making this rejection, the Examiner asserts that this reference has inherently demonstrated that the anti-angiogenic activity of FK506 is effective in treating a subject with a condition associated with unwanted angiogenesis.

For the reasons detailed below, the Appellants submit that Jiang et al. fails to anticipate the claimed invention. Specifically, the Appellants submit that Jiang et al. fail

to teach, either expressly or inherently, inhibition of angiogenesis in a host by administering a Ca^{2+}/calcineurin/NF-ATc inhibitory agent as is claimed.

Jiang et al. is drawn to testing whether FK506 prevents skin papilloma formation in an experimental mouse model. In this model, papilloma formation is induced on the skin of CD-1 mice by initiation with a single topical dose of 7,12-dimethylbenz[*a*]anthracene (DMBA) followed by repeated topical applications of 12-*O*-tetradecanoylphorbol-13-acetete (TPA) (i.e., twice weekly for 22 weeks). Using this model, Jiang et al. compared skin papilloma formation in mice in which FK506 was applied to the treated region 15 minutes prior to each application of TPA to those that received no FK506 pre-treatment. Their results indicate that FK506 pre-treatment of skin reduces papilloma formation, both in the number of mice that develop papillomas as well as the number of papillomas per mouse (in mice in which they develop).

In interpreting this data, the Examiner asserts that Jiang et al. has inherently demonstrated that the anti-angiogenic activity of FK506 is what is responsible for its ability to reduce papilloma formation in this system. The Appellants respectfully disagree.

To establish that a claim is inherently anticipated by a prior art reference, MPEP §2112 (IV) states:

> "To establish inherency, **the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill**. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). (emphasis added)
>
> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

With regard to the rejection of the claims in this Group, the "missing descriptive matter" in Jiang et al. is three-fold. First, Jiang et al. fails to teach that papilloma formation in the disclosed mouse model system requires angiogenesis. Second, Jiang et al. fails to teach that the inhibition of papilloma formation by FK506 in their model

system is due to inhibition of angiogenesis. And third, Jiang et al. fails to teach that the inhibition of papilloma formation by FK506 (or any agent) in their mouse model system is due to inhibition of Ca^{2+}/calcineurin/NF-ATc.

With regard to the first item above, the Appellants submit that the Examiner has failed to provide any extrinsic evidence to establish that papilloma formation in this mouse model requires angiogenesis (i.e., that inhibition of angiogenesis in this model system will necessarily inhibit papilloma formation). Rather, the Examiner has merely put forth, without extrinsic evidence, that there is a possibility that angiogenesis is a required element of papilloma formation in this mouse model. However, as stated in the excerpt above, inherency "*may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient*". In the absence of any extrinsic evidence, the Appellants submit that it does not necessarily flow that agents that inhibit angiogenesis will inhibit papilloma formation in this mouse model.

With regard to the second item above, the Appellants submit that the Examiner has failed to provide any extrinsic evidence to establish that the inhibitory effect of FK506 on papilloma formation in this mouse model is due to its anti-angiogenic properties. Indeed, it is virtually impossible for the Examiner to make such a claim given that he has failed even to provide extrinsic evidence to establish that angiogenesis is required for papilloma formation in the mouse model employed in Jiang et al. Rather, the Examiner has merely put forth, without any extrinsic evidence, that there is a possibility that FK506 inhibits papilloma formation in this mouse model by inhibiting angiogenesis. However, as stated in the excerpt above, inherency "*may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient*". In the absence of any extrinsic evidence, the Appellants submit that it does not necessarily flow that FK506 inhibits angiogenesis because it inhibits papilloma formation in this mouse model.

With regard to the third item above, the Appellants submit that the Examiner has failed to provide any extrinsic evidence to establish that the inhibitory effect of FK506 (or any agent) on papilloma formation in this mouse model is due to its inhibition of Ca^{2+}/calcineurin/NF-ATc. Rather, the Examiner has merely put forth that there is a

possibility that an agent that inhibits papilloma formation in this mouse model inhibits Ca^{2+}/calcineurin/NF-ATc. However, as stated in the excerpt above, inherency "*may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient*". Furthermore, not only is this assertion by the Examiner not supported by any extrinsic evidence, it is directly contradicted in the cited prior art reference. Jiang et al. state explicitly in the *Introduction* section (and elsewhere) that papilloma formation in this mouse model is inhibited by agents that do not inhibit Ca^{2+}/calcineurin/NF-ATc (i.e., do not have immunosuppressive activity, e.g. cyclosporin H). Specifically, in the *Introduction* section (page 67, left column, last paragraph), Jiang et al. state:

> Cyclosporine H (CsH), an immunologically inactive congener of CsA (16), however, also inhibits skin tumor promotion (17)... caused by TPA. **These findings suggest that the anti-tumor-promoting action of CsA is essentially unrelated to the immunosuppressive effect of this compound**. (emphasis added)

As is clear from this passage, the ability of an agent to inhibit papilloma formation in this mouse model is not necessarily related to its ability to inhibit Ca^{2+}/calcineurin/NF-ATc (i.e., its immunosuppressive activity). Therefore, the Appellants submit that it does not necessarily flow that the ability of FK506 (or any agent) to inhibit papilloma formation in this mouse model is due to inhibition of Ca^{2+}/calcineurin/NF-ATc.

The Examiner's position can be summarized as follows:

1. FK506 can inhibit Ca^{2+}/calcineurin/NF-ATc;

2. Jiang et al. teach that FK506 inhibits papilloma formation in a mouse model;

3. Therefore, Jiang et al. inherently teach that FK506 inhibits angiogenesis by inhibiting Ca^{2+}/calcineurin/NF-ATc.

However, as detailed above, the Examiner has provided no extrinsic evidence to substantiate such a conclusion. Specifically, the Examiner has failed to establish that: 1) papilloma formation in the mouse model used in Jiang et al. requires angiogenesis; 2) the ability of FK506 to inhibit papilloma formation in the mouse model used in Jiang et al. is due to its anti-angiogenic activity; and 3) that the ability of FK506 (or any agent) to inhibit papilloma formation in the model system used in

Jiang et al. is due to its ability to inhibit Ca^{2+}/calcineurin/NF-ATc. Indeed, Jiang et al. explicitly contradicts element 3 (i.e., agents that do not inhibit Ca^{2+}/calcineurin/NF-ATc can inhibit papilloma formation in this model system).

Therefore, by failing to provide any extrinsic evidence that remedies the significant deficiencies in the teachings of Jiang et al., the Examiner has failed to establish that the claims of this Group are inherently anticipated by this reference.

Group II: Claims 15-18, 40 and 44

As described above, independent Claim 15 is drawn to inhibiting tumor growth in a host having a neoplastic disease condition by systemically administering an effective amount of a Ca^{2+}/calcineurin/NF-ATc inhibitory agent. Claims that dependent from Claims 15 are drawn to the use of specific Ca^{2+}/calcineurin/NF-ATc inhibitory agents (e.g., cyclosporin, FK506, and rapamycin).

The Examiner has rejected the claims of this Group as being anticipated by Jiang et al. In making this rejection, the Examiner asserts that this reference has inherently demonstrated that FK506 is effective in inhibiting tumor growth in a subject having a neoplastic disease condition as is claimed in this Group.

For the reasons detailed below, the Appellants submit that Jiang et al. fails to inherently anticipate the claimed invention. Specifically, the Appellants submit that Jiang et al. fail to teach, either expressly or inherently, inhibition of tumor growth in a host by administering a Ca^{2+}/calcineurin/NF-ATc inhibitory agent as is claimed.

With regard to the rejection of the claims in this Group, the "missing descriptive matter" in Jiang et al. is two-fold. First, Jiang et al. fails to teach that agents that inhibit papilloma formation in this model system also can inhibit tumor growth. Second, Jiang et al. fails to teach that the inhibition of papilloma formation by FK506 (or any agent) in their mouse model system is due to inhibition of Ca^{2+}/calcineurin/NF-ATc.

With regard to the first item, the Appellants submit that Jiang et al. is drawn exclusively to determining the effect of FK506 on papilloma formation and not to the growth of existing tumors. Jiang et al. make no statement nor draw any conclusion from their experiments regarding the effect of any agent on tumor growth. Jiang et al. are clearly cognizant of the fact that their experimental design precludes them from drawing such conclusions and instead restrict interpretation of their data to the

effect of FK506 on papilloma formation. As such, in rejecting the claims of this Group, the Examiner has merely put forth, without any extrinsic evidence, that there is a possibility that inhibition of papilloma formation by FK506 in the mouse model employed by Jiang et al. is directly related to the ability of an agent to inhibit tumor growth. However, as stated in the MPEP excerpt in the previous section, inherency "*may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient*". In the absence of any extrinsic evidence, the Appellants submit that it does not necessarily flow that agents that inhibit papilloma formation in this mouse model will inhibit tumor growth.

With regard to the second item, the Appellants submit that the Examiner has failed to provide any extrinsic evidence to establish that the inhibitory effect of FK506 (or any agent) on papilloma formation in this mouse model is due to its inhibition of Ca^{2+}/calcineurin/NF-ATc. Rather, the Examiner has merely put forth that there is a possibility that FK506 (or any agent) inhibits papilloma formation in this mouse model by inhibiting Ca^{2+}/calcineurin/NF-ATc. However, as stated in the MPEP excerpt in the previous section, inherency "*may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient*". Furthermore, not only is this possibility not supported by any extrinsic evidence, it is directly contradicted in the cited prior art reference. Jiang et al. state explicitly that papilloma formation in this mouse model is inhibited by agents that do not inhibit Ca^{2+}/calcineurin/NF-ATc (i.e., do not have immunosuppressive activity, e.g. cyclosporin H) (see citation from Jiang et al. in the previous section). In the absence of any extrinsic evidence, the Appellants submit that it does not necessarily flow that the ability of FK506 (or any agent) to inhibit papilloma formation in this mouse model is due to inhibition of Ca^{2+}/calcineurin/NF-ATc.

The Examiner's position can be summarized as follows:

1. FK506 can inhibit Ca^{2+}/calcineurin/NF-ATc;

2. Jiang et al. teach that FK506 inhibits papilloma formation in a mouse model;

3. Therefore, Jiang et al. inherently teach that FK506 inhibits tumor growth by inhibiting Ca^{2+}/calcineurin/NF-ATc.

However, as detailed above, the Examiner has provided no extrinsic evidence to substantiate such a conclusion. Specifically, the Examiner has failed to establish that: 1) agents that inhibit papilloma formation in the model system used in Jiang et al. will necessarily inhibition tumor growth; and 2) inhibition of papilloma formation by FK506 (or any agent) in the mouse model system used in Jiang et al. is due to inhibition of Ca^{2+}/calcineurin/NF-ATc. Indeed, Jiang et al. explicitly contradicts the second element (i.e., agents that do not inhibit Ca^{2+}/calcineurin/NF-ATc can inhibit papilloma formation in this model system).

Therefore, by failing to provide any extrinsic evidence that remedies the significant deficiencies in the teachings of Jiang et al., the Examiner has failed to establish that the claims of this Group are inherently anticipated by this reference.

In view of the discussion above, the Appellants submit that Jiang et al. fail to anticipate the claims of either Group I or Group II, either expressly or inherently, and respectfully request reversal of this rejection.

II. Claims 36-44, 46 and 47 are not obvious under 35 U.S.C. § 103(a) over Jiang et al. (Carcinogenesis 1993 14:67) in view of Flanagan et al. (Nature 1991 352:803).

It is respectfully submitted that the Examiner's *prima facie* case of obviousness is deficient because the combined teachings of the cited prior art fail to render the claimed invention obvious.

With regard to establishing a *prima facie* case of obviousness, MPEP§2143 states:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Appellants submit that the combined teachings of Jiang et al. and Flanagan et al. fail to teach or suggest each and every element of the claimed invention.

Group I: Claims 36-39

As noted above, the claims of this Group are drawn to inhibiting angiogenesis in a host having a condition associated with unwanted angiogenesis by administering a Ca2+/calcineurin/NF-ATc inhibitory agent (i.e., rapamycin, cyclosporin, cyclosporin A or derivative/mimetics thereof).

The Examiner asserts that Jiang et al. teaches all elements of the claims of this Group except the use of rapamycin or cyclosporin to inhibit angiogenesis. To remedy this deficiency, the Examiner cites Flanagan et al. which assertedly teaches that FK506, rapamycin and cyclosporin have similar biologic activity, and thus one of skill in the art would be motivated to replace FK506 (assertedly taught by Jiang et al.) with either cyclosporin or rapamycin.

With regard to teaching or suggesting a claimed invention, MPEP § 2143.02 states:

> **2143.02 Reasonable Expectation of Success Is Required**
> Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)

As discussed in detail above, the Appellants submit that Jiang et al. fails to teach inhibition of angiogenesis in a host by administering an effective amount of a Ca^{2+}/calcineurin/NF-ATc inhibitory agent. Without repeating the entirety of the argument, the Appellants submit that the Examiner <u>failed</u> to establish that: 1) papilloma formation in the mouse model used in Jiang et al. requires angiogenesis; 2) the ability of FK506 to inhibit papilloma formation in the mouse model used in Jiang et al. is due to its anti-angiogenic activity; and 3) that the ability of FK506 (or any agent) to inhibit papilloma formation in the model system used in Jiang et al. is due to its ability to inhibit Ca^{2+}/calcineurin/NF-ATc. Indeed, the Appellants note that Jiang et al. <u>explicitly</u> state that agents that <u>do not</u> inhibit Ca^{2+}/calcineurin/NF-ATc can inhibit papilloma formation in their model system.

Therefore, the Appellants submit that Jiang et al. fail to teach <u>or even suggest</u> that angiogenesis can be inhibited by administering a Ca^{2+}/calcineurin/NF-ATc inhibitory agent. Specifically, Jiang et al. fail to provide a <u>reasonable expectation of success</u> to one of ordinary skill in the art that administration of a Ca^{2+}/calcineurin/NF-ATc inhibitory

agent (i.e., rapamycin, cyclosporin, cyclosporin A or derivative/mimetics thereof) will inhibit angiogenesis as is claimed.

Flanagan et al. is cited by the Examiner merely for its asserted teaching that FK506, cyclosporin and rapamycin have similar biologic activity, and thus one of skill in the art would think to use one in place of the other. However, this asserted teaching fails to remedy the fundamental deficiencies in Jiang et al. in making the claimed invention obvious. Namely, Flanagan et al. fails to teach or suggest inhibition of angiogenesis in a host by administration of an effective amount of a Ca^{2+}/calcineurin/NF-ATc inhibitory agent (i.e., rapamycin, cyclosporin, cyclosporin A or derivative/mimetics thereof).

Group II: Claims 40-44

As noted above, the claims of this Group are drawn to inhibiting tumor growth in a host having a neoplastic disease condition by administering a Ca2+/calcineurin/NF-ATc inhibitory agent (i.e., rapamycin, cyclosporin, cyclosporin A or derivative/mimetics thereof).

The Examiner asserts that Jiang et al. teaches all elements of the claims of this Group except the use of rapamycin or cyclosporin (and derivatives) to inhibit tumor growth. To remedy this deficiency, the Examiner cites Flanagan et al. which assertedly teaches that FK506, rapamycin and cyclosporin have similar biologic activity, and thus one of skill in the art would be motivated to replace FK506 (assertedly taught by Jiang et al.) with either cyclosporin or rapamycin.

As discussed in detail above, the Appellants submit that Jiang et al. fails to teach inhibition of angiogenesis in a host by administering an effective amount of a Ca^{2+}/calcineurin/NF-ATc inhibitory agent. Without repeating the entirety of the argument, the Appellants submit that the Examiner has failed to establish that: 1) agents that inhibit papilloma formation in the model system used in Jiang et al. will necessarily inhibition tumor growth; and 2) inhibition of papilloma formation by FK506 (or any agent) in the mouse model system used in Jiang et al. is due to inhibition of Ca^{2+}/calcineurin/NF-ATc. Indeed, Jiang et al. explicitly contradicts the second element (i.e., agents that do not inhibit Ca^{2+}/calcineurin/NF-ATc can inhibit papilloma formation in this model system).

Therefore, the Appellants submit that Jiang et al. fail to teach or even suggest that tumor growth can be inhibited by administering a Ca^{2+}/calcineurin/NF-ATc inhibitory agent. Specifically, Jiang et al. fail to provide a reasonable expectation of success to one of ordinary skill in the art that administration of a Ca^{2+}/calcineurin/NF-ATc inhibitory agent (i.e., rapamycin, cyclosporin, cyclosporin A or derivative/mimetics thereof) will inhibit tumor growth as is claimed.

Flanagan et al. is cited by the Examiner merely for its asserted teaching that FK506, cyclosporin and rapamycin have similar biologic activity, and thus one of skill in the art would think to use one in place of the other. However, this asserted teaching fails to remedy the fundamental deficiencies in Jiang et al. in making the claimed invention obvious. Namely, Flanagan et al. fails to teach or suggest inhibition of tumor growth in a host by administration of an effective amount of a Ca^{2+}/calcineurin/NF-ATc inhibitory agent (i.e., rapamycin, cyclosporin, cyclosporin A or derivative/mimetics thereof).

Group III: Claim 46

Claim 46, drawn to a drawn to a method of inhibiting angiogenesis in a host having a condition associated with unwanted angiogenesis by administering to the subject an effective amount of a cyclosporin.

The Examiner asserts that Jiang et al. teaches all elements of the claims of this Group except the use of cyclosporin to inhibit angiogenesis. To remedy this deficiency, the Examiner cites Flanagan et al. which assertedly teaches that FK506 and cyclosporin have similar biologic activity, and thus one of skill in the art would be motivated to replace FK506 (assertedly taught by Jiang et al.) with cyclosporin.

Similar to the arguments for Group I above, the Appellants submit that Jiang et al. fails to teach inhibition of angiogenesis in a host by administering an effective amount of a cyclosporin. With regard to Claim 46, the Appellants submit that the Examiner failed to establish that: 1) papilloma formation in the mouse model used in Jiang et al. requires angiogenesis; and 2) the ability of FK506 to inhibit papilloma formation in the mouse model used in Jiang et al. is due to its anti-angiogenic activity.

Therefore, the Appellants submit that Jiang et al. fail to teach or even suggest that angiogenesis can be inhibited by administering a FK506 because the model

employed by Jiang et al. does not provide an accurate readout of the anti-angiogenic properties af an agent. As suc, Jiang et al. fail to provide a reasonable expectation of success to one of ordinary skill in the art that administration of FK506 to a host will inhibit angiogenesis.

Flanagan et al. is cited by the Examiner merely for its asserted teaching that FK506 and cyclosporin have similar biologic activity, and thus one of skill in the art would think to use one in place of the other. However, this asserted teaching fails to remedy the fundamental deficiencies in Jiang et al. in making the claimed invention obvious. Namely, Flanagan et al. fails to teach or suggest inhibition of angiogenesis in a host by administration of an effective amount of FK506 (or any related agent, e.g., rapamycin, cyclosporin, etc.).

Group IV: Claim 47

Claim 47, drawn to a drawn to a method of inhibiting tumor growth in a host having a neoplastic disease condition by administering to the subject an effective amount of a cyclosporin.

The Examiner asserts that Jiang et al. teaches all elements of the claims of this Group except the use of cyclosporin to inhibit tumor growth. To remedy this deficiency, the Examiner cites Flanagan et al. which assertedly teaches that FK506 and cyclosporin have similar biologic activity, and thus one of skill in the art would be motivated to replace FK506 (assertedly taught by Jiang et al.) with cyclosporin.

Similar to the arguments for Group II above, the Appellants submit that Jiang et al. fails to teach inhibition of angiogenesis in a host by administering an effective amount of a cyclosporin. With regard to Claim 46, the Appellants submit that the Examiner failed to establish that agents that inhibit papilloma formation in the model system used in Jiang et al. will necessarily inhibition tumor growth. The Examiner is merely making this assertion without any supporting evidence. As noted above, the experimental design used in Jiang et al. is not drawn to determining the effect of FK506 on established tumor growth. Rather, as stated repeatedly in Jiang et al., the studies are designed solely to determine the ability of an agent to inhibit papilloma formation in a mouse model.

Therefore, the Appellants submit that Jiang et al. fail to teach or even suggest

that angiogenesis can be inhibited by administering a FK506 because the model employed by Jiang et al. does not provide an accurate readout of the tumor growth-inhbitning properties of an agent. As such, Jiang et al. fail to provide a reasonable expectation of success to one of ordinary skill in the art that administration of FK506 to a host will inhibit tumor growth.

Flanagan et al. is cited by the Examiner merely for its asserted teaching that FK506 and cyclosporin have similar biologic activity, and thus one of skill in the art would think to use one in place of the other. However, this asserted teaching fails to remedy the fundamental deficiencies in Jiang et al. in making the claimed invention obvious. Namely, Flanagan et al. fails to teach or suggest inhibition of tumor growth in a host by administration of an effective amount of FK506 (or any related agent, e.g., rapamycin, cyclosporin, etc.).

In view of the arguments above, the Appellants submit that the combined teachings of Jiang et al. and Flanagan et al. fail to make obvious the claims of Groups I-IV and respectfully request reversal of this rejection.

SUMMARY

I. Claims 8-11, 15-18, 35, 37, 39, 40 and 44 are not anticipated under 35 U.S.C. § 102(b) by Jiang et al. (Carcinogenesis 1993 14:67) because Jiang et al. fail to teach or suggest inhibition of unwanted angiogenesis or tumor growth in a host by administering an effective amount of a Ca^{2+}/calcineurin/NF-ATc inhibitory agent as is claimed.

II. Claims 36-44, 46 and 47 are not obvious under 35 U.S.C. § 103(a) over Jiang et al. (Carcinogenesis 1993 14:67) in view of Flanagan et al. (Nature 1991 352:803) because Flanagan et al. fail to remedy the fundamental deficiencies in the teachings of Jiang et al.: namely, inhibition of unwanted angiogenesis or tumor growth in a host by administering an effective amount of a Ca^{2+}/calcineurin/NF-ATc inhibitory agent or a cyclosporine.

RELIEF REQUESTED

The Appellants respectfully request that the rejection of Claims 8-11, 15-18, 35, 37, 39, 40 and 44 under 35 U.S.C. § 102 and the rejection of Claims 36-44, 46 and 47 under 35 U.S.C. § 103 be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: 4-28-06

By: _____
David C. Scherer, Ph.D.
Registration No. 56,993

Date: 4.28.06

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CLAIMS APPENDIX

8. A method of inhibiting angiogenesis/vascular development in a host having a condition associated with unwanted angiogenesis, said method comprising:

systemically administering to said host an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent to inhibit angiogenesis/vascular development in said host having a condition associated with unwanted angiogenesis.

9. The method according to Claim 8, wherein said agent is an NF-ATc antagonist.

10. The method according to Claim 9, wherein said agent inhibits phosphorylation of NF-ATc.

11. The method according to Claim 10, wherein said agent inhibits NF-ATc phosphorylation by binding to calcineurin.

15. A method of inhibiting tumor growth in a host having a neoplastic disease condition, said method comprising:

systemically administering to said host having a neoplastic disease condition an effective amount of a Ca2+/calcineurin/NF-ATc inhibitory agent to inhibit tumor growth in said host.

16. The method according to Claim 15, wherein said agent is an NF-ATc antagonist.

17. The method according to Claim 16, wherein said agent inhibits phosphorylation of NF-ATc.

18. The method according to Claim 16, wherein said agent inhibits NF-ATc phosphorylation by binding to calcineurin.

35. The method according to Claim 8, wherein said agent is FK506 or a synthetic mimetic thereof.

36. The method according to Claim 8, wherein said agent is rapamycin or a synthetic mimetic thereof.

37. The method according to Claim 8, wherein said agent is a cyclosporin.

38. The method according to Claim 37, wherein said cyclosporin is cyclosporin A.

39. The method according to Claim 38, wherein said cyclosporin is a synthetic derivative or mimetic of cyclosporin A.

40. The method according to Claim 15, wherein said agent is FK506 or a synthetic mimetic thereof.

41. The method according to Claim 15, wherein said agent is rapamycin or a synthetic mimetic thereof.

42. The method according to Claim 15, wherein said agent is a cyclosporin.

43. The method according to Claim 42, wherein said cyclosporin is cyclosporin A.

44. The method according to Claim 42, wherein said cyclosporin is a synthetic derivative or mimetic of cyclosporin A.

46. A method of inhibiting angiogenesis/vascular development in a host having a condition associated with unwanted angiogenesis, said method comprising:

administering to said host an effective amount of a cyclosporin to inhibit angiogenesis/vascular development in a host having a condition associated with unwanted angiogenesis.

47. A method of inhibiting tumor growth in a host having a neoplastic disease condition, said method comprising:

administering to said host an effective amount of a cyclosporin to inhibit tumor growth in said host having a neoplastic disease condition.

EVIDENCE APPENDIX

No evidence that qualifies under this heading has been submitted during the prosecution of this application, and as such it is left blank.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.